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Transplanting the elderly: Balancing aging with histocompatibility

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A B S T R A C T

Across the world, the proportions of senior citizens (i.e. those ≥65 years) increase rapidly and are predicted to constitute over 25% of the general population by 2050. In 2012 already 48% of the population with end stage renal disease (ESRD) was aged 65 years or older. Transplantation is considered the preferred treatment option for ESRD offering survival advantage over long-term dialysis in the majority of patients. Indeed, acceptable outcomes have been documented for selected patients over the age of 70 years or even cases over 80 years. The reality of organ scarcity and prolonged waiting times for a deceased donor kidney transplantation, however, indicate that at best 50% of the selected elderly may have realistic expectations to receive a timely transplant offer. By choice or medical selection, access to transplantation also decreases with increasing age. In order to expedite the chance for elderly to receive a kidney transplant dedicated allocation systems have been developed. These allocation systems, like the Eurotransplant Senior Program (ESP), support preferential local allocation of kidneys from older donors to older patients in order to match recipient and graft life while disregarding histocompatibility for HLA antigens. The consequence has been more acute rejection episodes and an increase in immunosuppressive load. In the elderly, the most common cause of graft loss is death with functioning graft and death from infectious diseases is one of the dominant causes. The Eurotransplant Senior DR-compatible Program (ESDP) was designed to further improve the perspective of successful transplantation in the elderly in terms of life and quality of life by re-introducing matching criteria for HLA-DR in the old-for-old algorithm.

1. Introduction

Recent data from the World Urbanization Prospects indicate that the proportion of individuals over 60 years will double between 2000 and 2050 from 11% to 22%. In absolute numbers this means an expected increase from 605 million to 2 billion individuals aged 60 years or older [1].

Although the incidence of end stage renal disease (ESRD) appears to have reached a plateau over the past two to three years, the annual numbers of ESRD incident cases have been rising for many years, especially in patients of 65 years and older. The United States Renal Data System shows an increase in prevalence of ESRD between 2000 and 2012 of 30% in the population between 65 and 74 years and the group ≥75 years even increased 50%. In 2012, 48% of the incident ESRD population was older than 65 years, and 24% were ≥75 years [2]. In the Netherlands we see similar data according to the Dutch National Renal Replacement Database (Renine). These data are summarized in Fig. 1.

Because there is a survival benefit of transplantation over long-term dialysis, renal transplantation is the preferred treatment for ESRD patients and most guidelines state that there should be no upper (calendar) age limit for transplantation. When evaluating older ESRD patients for transplantation, however, several age specific factors need to be taken into account. In the context of organ shortage, the debate continues whether elderly should be placed on the regular waiting list or preferentially on special designed allocation systems like the Eurotransplant Senior Program (ESP). In this review we will elaborate on factors important to the older transplant recipient including patient and graft survival, impact of age on the immune system, consequences of using older kidney donors, late graft failure and the role for humoral immunity and the allocation system reconsidering the importance of histocompatibility for HLA antigens in this context.

2. The aging ESRD patient

The survival benefit of transplantation over long-term dialysis includes all causes of ESRD (e.g. glomerulonephritis, hereditary renal disease, diabetes and hypertension) and all age categories of patients. The magnitude, however, of the improved patient survival is not uniform across patient subgroups such as the elderly and/or those with diabetes [3–9]. The landmark study of Wolfe et al. showed that the projected years of life remaining almost doubled for those who received a transplant as compared to waitlisted counterparts remaining on dialysis. The greatest difference was observed in the group aged 20–39 years, but patients between 60 and 74 years still had an improvement of their cumulative survival rate after the first year of transplantation of approximately 4 years and a decrease in the long-term risk of

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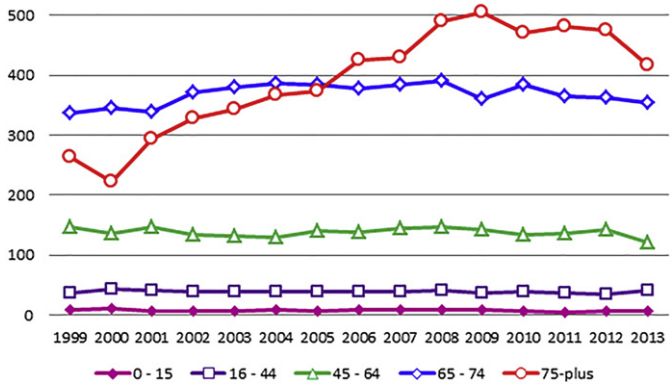

Fig. 1. The aging ESRD population in the Netherlands: Incidence per million population.

death of 61%. A sub-analysis of transplant recipients ≥70 years of age documented a 56% lower long-term mortality risk (>18 months) compared with their waitlisted counterparts. Additional data from the Renine registry in Fig. 2A show the 5-year patient survival according to age category of patients who started renal replacement therapy (RRT) between 2002 and 2007. In line with results from the Scientific Registry of Transplant Recipients (SRTR), the elderly carry a significant risk not to survive long enough before a kidney is offered for transplantation.

Older transplant recipients are a selected patient group with overall good patient and graft survival. With the current standard immunosuppressive regimens patient survival rates are 80–90%, 70% and 50% at 1, 5 and 10 years respectively [10–13]. Several studies have documented that death-censored graft survival in the elderly is comparable or even better than younger transplant recipients [14–17]. It is not surprising that with increasing age, mortality rates after transplantation are higher. The main causes of death among elderly transplant recipients are cardiovascular and infectious diseases [18,19]. Nearly 50% of graft loss in older patients occurred because of death versus only 15% in younger patients [12,20]. Patients older than 65 years are seven times more likely to die with a functioning graft compared with patients between 18 and 29 years [21].

2.1. Access to renal replacement therapy for elderly

Because successful kidney transplantation improves both longevity and quality of life [7,22], the numbers of waitlisted patients almost doubled between 2002 and 2012 [23]. In 2012 the active waiting list was 2.7 times the supply of donor kidneys and mean waiting time increased to 3.6 years. From patients listed in 2010 over 50% had not undergone transplantation in 2013 [24]. Since advanced age is no contra-indication for transplantation, the proportions of older ESRD patients on the waiting list also increased from 12% to 21% in the last decade [23,24]. At present approximately 23,228 patients older than 65 years are on the waiting list for a kidney transplant in the US.

Although the absolute numbers of elderly on the waiting list increased, the percentage of elderly with ESRD placed on the waiting list decreases with increasing age. In 2009, 21% of patients between 18 and 39 years and 16% of patients between 40 and 59 years were listed for kidney transplantation in the US. Listing decreased to only 3.4% of the ESRD patients above 70 years and 0.5% of those 80 years and older [25]. This decrease in transplantation rate is also shown in Fig. 2 where we compared patient survival in the Netherlands 5 years after initiation of RRT and the transplant rate according to different age categories. Patients aged over 65 years had both the lowest survival rates while on dialysis and the lowest transplant rate. Under the age of 46 years over 70% of patients with ESRD received a kidney transplant, while over the age of 64 years or 74 years only 25% and 3% were transplanted, respectively. Several studies report that the likelihood of being waitlisted or actually receiving a transplant, decreased with the presence of more comorbid conditions [26–28]. There are however also studies that have suggested that elderly were not waitlisted although no formal contra-indications were found according to current guidelines [29,30].

2.2. Immunologic changes and the effect on rejection with aging

It is generally assumed that the immune system undergoes structural and functional changes with aging. In the setting of solid organ transplantation, the most important changes concern qualitative alterations in T-cell activation and/or quantitative differences in T-cell subsets. The co-stimulatory pathways of alloantigen recognition appear to be hampered in older patients, at least in comparison to significantly younger individuals, with a shift from naïve to a more memory T cell phenotype [31–34]. This results in decreased immune reactivity in the older individual and, at least theoretically, may have impact on the risk of experiencing an acute rejection episode after organ transplantation. Meier-Kriesche et al. reported a reduction in the incidence of acute rejection of approximately 20% in patients >65 years compared to recipients between 18 and 29 years [35] and also Cecka reported a decrease in

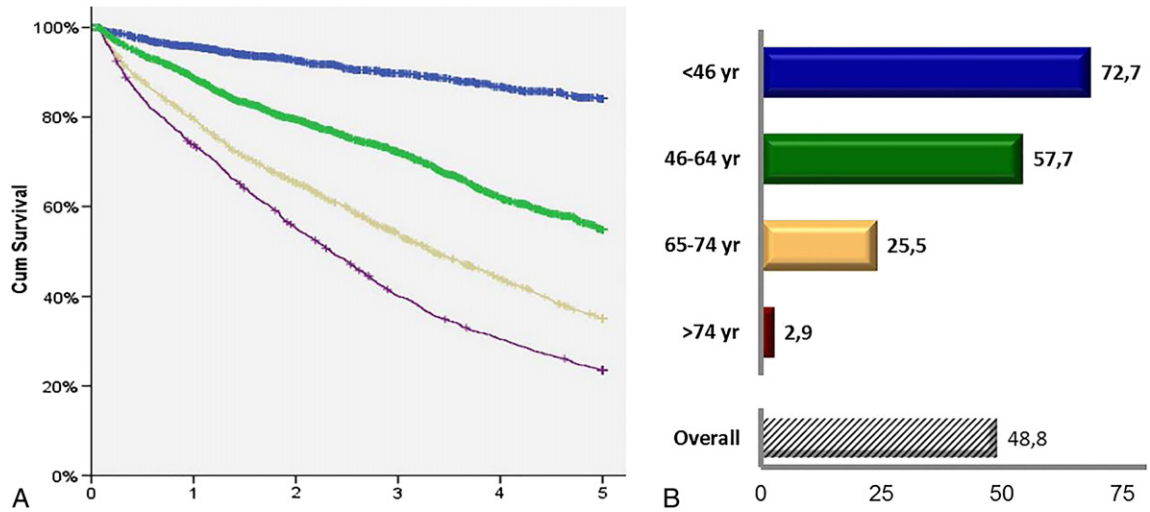

Fig. 2. Patient survival according to age category. (A) While on dialysis up to 5 years after initiation, and (B) transplant rates within 5 years after initiation of dialysis (data extracted from the Dutch Organ Transplant Registry).